



The Egyptian Society of Chest Diseases and Tuberculosis
Egyptian Journal of Chest Diseases and Tuberculosis

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ORIGINAL ARTICLE

The golden factor in adherence to inhaled corticosteroid in asthma patients

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Received 1 June 2013; accepted 21 July 2013

Available online 19 August 2013

KEYWORDS

Patient education;
Adherence;
Bronchial asthma;
ICS

Abstract *Objectives:* Adherence to therapy is very important and many factors could be responsible for this issue. Suboptimal adherence to asthma therapy is a major contributor to poor asthma outcomes. Our aim is to find out the most important factor responsible for adherence to therapy in bronchial asthma patients.

Subjects and methods: The study included 143 patients with persistent bronchial asthma. Factors that may affect adherence to therapy were studied. These factors included age, sex, residence, level of education, proper asthma education and whether inhaled corticosteroid (ICS) was taken alone, with long acting β_2 agonist (LABA) in separate devices or with LABA in a combined form. Adherence to ICS was determined according to Medication Rating Scale.

Results: We found that 55.3% of patients that received asthma education were adherent to ICS while only 21% of patients that did not receive asthma education were adherent to ICS therapy. The difference was statistically highly significant ($p = 0.003$). Other factors do not significantly affect adherence to ICS. Patients that used combined ICS with LABA in the same device were significantly more adherent to therapy (60.25%) than patients that used the same combination in 2 separate devices (34.5%). All patients with well controlled asthma were adherent to ICS, while 47.5% of uncontrolled patients was adherent. Comparison between level of control and adherence to ICS was highly significant ($p = 0.003$).

Conclusion: This study showed how different factors may modulate adherence to asthma treatment and confirmed the importance of patient education in increasing adherence to asthma therapy.

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Peer review under responsibility of The Egyptian Society of Chest Diseases and Tuberculosis.



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Introduction

Adherence to (or compliance with) a medication regimen is generally defined as the extent to which patients take medications as prescribed by their health care providers. The word “adherence” is preferred by many health care providers, because “compliance” suggests that the patient is passively following the doctor’s orders and that the treatment plan is not based on a therapeutic alliance or contact established between the patient and the physician. Both terms are imperfect and uninformative

descriptions of medication-taking behavior. Unfortunately, applying these terms to patients who do not consume every pill at the desired time can stigmatize these patients in their future relationships with health care providers. The language used to describe how patients take their medications needs to be reassessed, but these terms are still commonly used [1].

Asthma is a significant public health problem, particularly among inner city populations. It is a leading cause of preventable emergency room visits and hospitalizations. Considerable efforts have been directed at promoting appropriate self-management behaviors in order to improve asthma outcomes [2]. The first difficulty is to explain to the patient that asthma is a chronic disease and has a wide margin of variability [3]. In a great number of cases the patients do not perceive the chronic nature of their illness, its long term outcome and the significance of long-term therapy. The real problem for the management of asthma is the adherence to treatment and self-management [4].

It has been estimated that the regular use of inhaled corticosteroid (ICS) could reduce asthma hospitalizations by as much as 80%, and that the risk of death from asthma decreases by 21% for each additional ICS canister used in the previous year [5]. Despite such potential, patients with asthma appear to adhere poorly to prescribed ICS medications [6].

There have been many delivery systems developed for ICS, each with advantages and disadvantages. Among these, the two most frequently used devices are the pressurized metered dose inhaler and the dry powder inhaler. For ICS to be effective, good inhaler technique and adequate adherence are important. With regard to technique, specific steps and good coordination are necessary for the proper use of these devices. A less than optimal technique can result in decreased drug delivery and potentially reduced efficacy [7].

Patient education, pulmonary function monitoring, environmental control and pharmacotherapy are four main pillars of asthma management [8]. Because of its several advantages, inhalation therapy has become the treatment of first choice in the western countries, though deficiencies exist there also. Studies of adults and children have shown compliance rates of around 50% with the taking of regular preventive therapy (around 35% in USA and 41% in Europe) [9].

Adherence to therapies is a primary determinant of treatment success. Poor adherence attenuates optimum clinical benefits and therefore reduces the overall effectiveness of health systems, yet it is estimated that in developed countries, only 50% of patients who suffer from chronic diseases adhere to treatment recommendations [10]. Coordinating multiple components of the healthcare system is necessary to improve adherence and clinical outcomes. For instance, psychological problems such as depression and anxiety disorders are common among asthma patients and their primary caregivers, and may present significant barriers to adherence [11].

Although collaborative efforts to improve adherence may be costly in the short run, the long-term cost savings gained by improved adherence can exceed the cost of adherence promotion. This makes adherence promotion a worthy "investment" in managing asthma outcomes [12].

Asthma education is an essential part of the treatment of this disease. Health care professionals must establish a partnership with the patient with asthma and the patient's family to devise a plan of care with which the patient voluntarily will comply. When the partnership is based on mutual trust and cooperation, the clinician can direct asthma care that is consis-

tent with current expert guidelines. Educational interventions should be meaningful to the patient, considering patient's needs, and sensitive to the patient's cultural influences [13].

Subjects and method

One hundred and forty-three asthmatics that attended the out-patient clinic in El Minia and Assiut University hospitals were included. Enrolled patients were under treatment with ICS either alone or combined with LABA. Complete medical history was taken every visit in order to determine the level of control according to the control level in GINA guidelines. Factors that may affect adherence to therapy were studied. These factors included age, sex, residence, level of education, proper asthma education and whether ICS was used alone, with LABA in separate devices or with LABA in a combined form. One hundred and twelve asthmatic patients attended the asthma education program sessions. Duration of asthma education program was 2 months and its basic components included the basics of asthma, diagnosis of asthma, types of treatment available, advantages of inhalation therapy, role of 'relievers' and 'preventers', removing misconceptions. The rest of the patients [31] were prescribed inhalers by other centers and by assessing the educational programs they got we reached the conclusion that some patients did not get education at all and the others got insufficient education.

Basic components of asthma education program [14]

- Basics of asthma
 - Asthma is a fully controllable ailment, though not curable as yet.
 - Airway inflammation is the main defect in asthma.
 - Steroid inhalers, taken regularly with proper technique are best tools to tackle this inflammation.
 - Regular drug intake curtails the cost of therapy and progression of the disease.
 - All these aspects should be covered in simple language citing common examples.
- Diagnosis of asthma.
- Types of treatment available.
- Advantages of inhalation therapy.
- Role of 'relievers' and 'preventers'.
- Removing misconceptions: Patients may believe misconceptions about inhalation therapy that inhalation therapy may be dangerous and damage lungs and heart, must be the last resort, habit forming, higher cost and difficult to use in addition to steroid phobia which is present in most patients.
- Trigger avoidance (including drugs).
- Monitoring of asthma.
- Crisis recognition and management.
- Adopting a healthy life style.
- Patients should be motivated for adopting a healthy life style including smoking cessation, well-balanced diet, regular exercise and the avoidance of obesity.

Treatment checked repeatedly as incorrect use of inhalation devices is frequently observed at all levels. Misconceptions about asthma and its management, especially inhalation ther-

Table 1 Items of the Modified Morisky Scale [15].

Items	Response format
Do you sometimes forget to take your [health concern] pills?	Yes or No
People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your [health concern] medicine?	Yes or No
When you travel or leave home, do you sometimes forget to bring along your [health concern] medication?	Yes or No
Did you take your [health concern] medicine yesterday?	Yes or No
When you feel like your [health concern] is under control, do you sometimes stop taking your medicine?	Yes or No
Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your [health concern] treatment plan?	Yes or No
How often do you have difficulty remembering to take all your medications?	Never/ Rarely, Once in a while, Sometimes, Usually, All the time

The Modified Morisky scale yield a total score with a range of 0–7, with higher scores indicating higher adherence to medication. The scores of the Modified Morisky scale can be categorized as low compliers (< 6), medium compliers (= 6) and high compliers (= 7).

apy, should be discussed and dispelled at each visit. We used booklets, charts, and inhalation devices to explain how to use the devise. To determine adherence in asthmatic patients we use the Modified Morisky Scale (MMS) (Table 1).

We asked the patient each question and circle the corresponding “yes” or “no” response. The Modified Morisky scale yields a total score with a range of 0–7, with higher scores indicating higher adherence to medication. The scores of the Modified Morisky scale can be categorized as low compliers (< 6), medium compliers (= 6) and high compliers (= 7) [15].

Statistical analysis

Quantitative data were expressed as mean and standard deviation (mean \pm SD). Student’s “*t*” test was used to compare mean values of the two groups. Comparison between more than 2 groups was performed by using one way ANOVA test for parametric variables. Simple Pearson’s correlation coefficient was calculated to quantify the correlation between continuous variables and multiple stepwise regressions and was used to determine the variables that may correlate independently with Z-score BUA values. Statistical analysis was performed using (SPSS) 16 for Windows software.

Results

Sociodemographic data of the studied asthmatic patients were shown in Table 2. Comparison between adherent and non

Table 2 Sociodemographic data of the studied asthmatic patients.

Sociodemographic data	N (%)
<i>Sex</i>	
Male	40 (28)
Female	103 (72)
<i>Residence</i>	
Urban	79 (55.2)
Rural	64 (44.8)
<i>Level of education</i>	
University	62 (43.3)
Basic and secondary	24 (16.8)
Illiterate or read and write only	57 (39.9)
<i>Control level</i>	
Controlled	10 (7)
Partially controlled	93 (65)
Uncontrolled	40 (28)
<i>Adherence to ICS</i>	
Adherent	70 (49)
Not adherent	73 (51)
<i>Patient education</i>	
Present	112 (78.3)
Absent	31 (21.7)
Age (mean \pm SD) years	44.3 \pm 14.648

adherent patients showed that adherent patients were significantly older than non adherent. Other factors namely, sex, residence, and level of education showed no significant difference (Table 3). Table 4 showed that 55.3% of patients who received education were adherent to ICS while only 21% of patients who did not receive education were adherent to ICS therapy. The difference was statistically highly significant ($p = 0.003$). Table 5 showed a relation between methods of administration of ICS and adherence to treatment where more patients used combined ICS with LABA in the same device (group1) adherent to therapy (60.25%) than patients who used the same drugs in 2 separate devices (34.2%) (group 2) and patients who received ICS plus oral LABA (37.2%) (group 3). Table 6 showed the relation between the level of asthma control and adherence to treatment where 100% of well controlled patients were adherent to ICS, while 44.1% of partial controlled patients were adherent and 47.5% of uncontrolled patients were adherent. Comparison between level of control and adherence to ICS was highly significant (p value = 0.003).

Discussion

Adherence to treatment is an important part in treatment success. Adherence to ICS in asthmatic patients is a well documented issue in controlling the disease. In this study we compared factors that affect adherence to ICS in asthmatic patients and try to explain the most important factor that affects adherence. In our study adherence to asthma treatment was 49%. This result agreed with the observation of WHO which recorded that treatment compliance in chronic diseases was 50% [10]. In his study, Lacasse et al. 2005 [16] showed that compliance was 20–70%. In the other hand Al-Jabdali et al. 2007 [17] showed that compliance in their study was

Table 3 Relation between sociodemographic factors of asthmatic patients and adherence to ICS.

	Patients not adherent to ICS (<i>N</i> = 70) <i>N</i> (%)	Patient adherent to ICS (<i>N</i> = 73) <i>N</i> (%)	<i>p</i> Value
<i>Sex</i>			
Male (<i>N</i> = 40)	24 (60%)	16 (40%)	0.1
Female(<i>N</i> = 103)	46 (44.6%)	57 (55.4%)	
<i>Residence</i>			
Urban (<i>N</i> = 79)	43 (54.4%)	36 (45.6%)	0.1
Rural (<i>N</i> = 64)	27 (42.2%)	37 (57.8%)	
<i>Level of education</i>			
University (<i>N</i> = 62)	30 (48.4%)	32 (51.6%)	0.66
Basic and secondary (<i>N</i> = 24)	10 (41.7%)	14 (58.3%)	
Illiterate and (read and write) (<i>N</i> = 57)	30 (2.6%)	27 (47.4%)	
Age (mean ± SD) years	47.2 ± 13.642	41.6 ± 15.5	0.02*

* *p* Value < 0.05.**Table 4** Effect of patient education on adherence to ICS in asthmatic patients.

Adherence to ICS	Patient education		<i>p</i> Value
	With patient education	Without patient education	
Adherent, <i>N</i> (%)	62 (55.3%)	8 (21%)	0.003*
Not adherent, <i>N</i> (%)	50 (44.7%)	23 (79%)	
Total, <i>N</i> (%)	112 (100%)	31 (100%)	

* *p* Value < 0.05.**Table 5** Comparison between methods of ICS administration and adherence to therapy.

Methods of ICS administration	Adherence to ICS		<i>p</i> Value
	Adherent (<i>No</i> = 70)	Not adherent (<i>No</i> = 73)	
Group 1: (78, 100%) Patients used ICS and LABA in the same device	47 (60.25%)	31 (39.75%)	0.001
Group 2: (38, 100%) Patients used ICS and LABA in 2 separate devices	13 (34.2%)	25 (65.8%)	
Group 3: (27, 100%) patients used ICS alone or plus oral LABA	10 (37%)	17 (63%)	

Table 6 Relation between control level of asthmatic patients adherence to ICS.

Adherence to ICS	Control level			<i>p</i> Value
	Uncontrolled <i>N</i> (%)	Partial controlled <i>N</i> (%)	Well controlled <i>N</i> (%)	
Adherent	19 (47.5%)	41 (44.1%)	10 (100%)	0.003*
Not adherent	21 (52.5%)	52 (55.9%)	0	
Total	40 (100%)	93 (100%)	10 (100%)	

* *p* Value < 0.05.

reasonably high (62%), which may be a reflection of the fact that most of their patients has significant asthma and followed up in tertiary centers rather than primary centers.

In our study, patient gender did not affect treatment adherence as the difference between male and female adherence was

statistically not significant. The results of many studies discussed this issue were contradictory. Female patients were found by some researchers to have better compliance [18] while some studies suggested otherwise [19]. In addition, some studies could not find a relationship between gender and compli-

ance [20]. Our observation is consistent with another review on compliance that concluded that gender has not been found to influence compliance [21]. Gender may not be a good predictor of non-compliance because of inconsistent conclusions.

For a long time it was believed that the level of education of the patients is an important factor that affects adherence, surprisingly our study showed that the level of education did not affect adherence to ICS and was statistically insignificant. Several studies found that patients with higher educational level might have higher compliance [22,23], while some studies found no association [24]. Intuitively, it may be expected that patients with higher educational level should have better knowledge about the disease and therapy and therefore be more compliant. However, DiMatteo found that even highly educated patients may not understand their conditions or believe in the benefits of being compliant to their medication regimen [25]. Other researchers showed that patients with lower education level have better compliance [20]. Patients with lower educational level might have more trust in physicians' advice. From these results, it seems that educational level may not be a good predictor of therapeutic compliance.

This study showed that older patients tended to be more adherent to prescribed asthma medications than younger ones. We showed that older people might have more concern about their health than younger patients, so that older patients' non-compliance is non-intentional in most cases. As a result, if they can get the necessary help from healthcare providers or family members, they may be more likely to be compliant with therapies.

Some studies showed that older patients adhered more to treatment regimens than younger patients. However, a different outcome was seen in a different study where limited physical ability of elderly patients reduced adherence level. This limitation was due to social isolation, auditory and visual impairment, and health problems occurring among those taking a number of medications for different medical conditions [26].

In our study, asthma education significantly influences adherence to ICS therapy and the difference was statistically highly significant between patients that received asthma education and patients that did not receive this education. Rubin found that educating the patients about their diseased state and general comprehension of medications would increase their active participation in treatment [27]. Making sure patients understand the drug dosing regimen could also improve compliance. To make sure patients remember what was taught, written instructions work better than verbal ones, as patients often forget physician's advice and statements easily [28].

The result of the study of Al-Jahdali et al. 2007 raises the importance of the education program of the patient involved in asthma care to discuss with them the role of asthma medications, particularly ICS, and to correct common fears and misconceptions. Among the most common fears hindering regular ICS use was their potential to lead to addiction (60%) and worry from steroid side effects (41%) [17].

The simplicity of drug administration greatly increases adherence as the complexity significantly hinders it. If 2 or 3 different medications are prescribed with 2 or 3 different delivery methods (e.g. concurrent use of MDI and DPI) it may add to confusion in techniques and lead to poor adherence. In our study patients that received combined ICS and LABA in the same device (group1) were significantly more adherent to therapy than patients that used combined ICS and LABA in two separate devices (group2) and patients that used ICS plus oral LABA (group3).

Increasing dosing and frequency in asthma treatment was found to have an inverse correlation with adherence, as seen in a study that was conducted on 14 children with asthma, where inhaler compliance with twice, thrice- and four-times daily dosing was examined. The compliance rate was 71, 34 and 18 percent respectively. Hence, increase of complication in dosing regimen resulted in less compliant patients [29].

Medications with a convenient way of administration (e.g. oral medication) are likely to make patients compliant. Studies in asthma patients compared compliance between oral and inhaled asthma medications, and found patients had better compliance with oral medication. Likewise, difficulty in using inhalers contributes to non-compliance in patients with asthma [30].

Complex treatment is believed to threaten the patient's compliance. However, compliance does not seem to correlate with the number of drugs prescribed but the number of dosing times every day of all prescribed medications [29]. The rate of compliance decreased as the number of daily doses increased. This is illustrated by one study where compliance was assessed by pill counts and self-reports that showed that non-compliance increased with an increase in the frequency of prescribed dosing: 20% for once daily; 30% for twice daily; 60% for three times a day; and 70% for four times daily [31]. Thus, simplifying the medication dosing frequency could improve compliance markedly.

Achieving asthma control is central in optimizing patient quality of life and clinical outcome. This study showed that adherence to ICS therapy increases significantly the control level of asthma symptoms and offers more improvement of pulmonary function. The study of Al-Jahdali et al. 2007 reports that misconception of the role of ICS and fear of untoward side effects may reduce compliance to therapy, potentially resulting in poor asthma control and outcome and increased risk of severe asthma [17].

Conclusion

Among different factors that may modulate adherence to treatment in asthmatic patients, asthma education is the most important and golden factor in increasing adherence to ICS therapy.

Conflict of interest

None declared.

References

- [1] J.F. Steiner, M.A. Earnest, The language of medication-taking, *Ann. Intern. Med.* 132 (2000) 926–930.
- [2] M. Settings, Expert panel report 3 (EPR-3). Guidelines for the diagnosis and management of asthma – Summary report 2007, *J. Allergy Clin. Immunol.* 120 (2007) 94–138.
- [3] K.R. Chapman, L. Walker, S. Cluley, L. Fabbri, Improving patient compliance with asthma therapy, *Respir. Med.* 94 (2000) 2–9.
- [4] I. Baiardini, F. Braido, A. Giardini, G. Majani, C. Cacciola, A. Rogaku, et al, Adherence to treatment, *J. Investig. Allergol. Clin. Immunol.* 16 (4) (2006) 218–223.
- [5] S. Suissa, P. Ernst, S. Benayoun, M. Baltzan, B. Cai, Low-dose inhaled corticosteroids and the prevention of death from asthma, *N. Engl. J. Med.* 343 (5) (2000) 332–336.
- [6] M.G. Cochrane, M.V. Bala, K.E. Downs, J. Mauskopf, R.H. Ben-Josep, Inhaled corticosteroids for asthma therapy: patient

- compliance, devices, and inhalation technique, *Chest* 117 (2000) 542–550.
- [7] B.Y. Khassawneh, M.K. Al-Ali, K.H. Alzoubi, M.Z. Batarseh, S.A. Al-Safi, A.M. Sharara, et al, Handling of inhaler devices in actual pulmonary practice: Metered-dose inhaler versus dry powder inhalers, *Respir. Care* 53 (2008) 324–328.
 - [8] Indian guidelines of bronchial asthma in adults, *J. Assoc. Physicians India* 50 (2002) 461–501.
 - [9] J.A. Coultas, N.A. Gibson, J.Y. Paton, Measuring compliance with inhaled medication in asthma, *Arch. Dis. Child.* 67 (1992) 332–333.
 - [10] World Health Organization, Adherence to long-term therapies: Evidence for action, 2003.
 - [11] B.G. Bender, C rand medication non-adherence and asthma treatment cost, *Curr. Opin. Allergy Clin. Immunol.* 4 (2004) 191–195.
 - [12] M. Otsuki, M. Eakin, L.L. Arceneaux, et al, Prospective relationship between maternal depressive symptoms and asthma morbidity among inner-city African American children, *J. Pediatr. Psychol.* 35 (2010) 758–767.
 - [13] P.K. Musto, General principals of management: education, *Nurs. Clin. North Am.* 38 (4) (2003) 621–633.
 - [14] S.B. Rajinder, Patient education program for asthmatics: indian perspective, *Indian J. Chest Dis. Allied Sci.* 49 (2007) 93–98.
 - [15] D.E. Morisky, A. Ang, M. Krousel-Wood, H. Ward, Predictive validity of a medication adherence measure in an outpatient setting, *J. Clin. Hypertens.* 10 (2008) 348–354.
 - [16] Y. Lacasse, H. Archibald, P. Ernst, et al, Patterns and determinants of compliance with inhaled steroids in adults with asthma, *Can. Respir. J.* 12 (2005) 211–217.
 - [17] H.H. Al-Jahdali, A.I. Al-Zahrani, S.T. Al-Otaibi, I.S. Hassan, M.S. Al-Moamary, A.S. Al-Duhaim, A.A. Al-Shimemeri, A.S. Al-Dawood, Perception of the role of inhaled corticosteroids and factors affecting compliance among asthmatic adult patients, *Saudi Med. J.* 28 (4) (2007) 569–573.
 - [18] S. Choi-Kwon, S.U. Kwon, J.S. Kim, Compliance with risk factor modification: early-onset versus late-onset stroke patients, *Eur. Neurol.* 54 (2005) 204–211.
 - [19] R.P. Hertz, A.N. Unger, M.B. Lustik, Adherence with pharmacotherapy for type 2 diabetes: a retrospective cohort study of adults with employer-sponsored health insurance, *Clin. Ther.* 27 (2005) 1064–1073.
 - [20] V. Senior, T.M. Marteau, J. Weinman, Self-reported adherence to cholesterol-lowering medication in patients with familial hypercholesterolaemia: the role of illness perceptions, *Cardiovasc. Drugs Ther.* 18 (2004) 475–481.
 - [21] S.A. Vic, C.J. Maxwell, D.B. Hogan, Measurement, correlates, and health outcomes of medication adherence among seniors, *Ann. Pharmacother.* 38 (2004) 303–312.
 - [22] A.J. Apter, S.T. Reisine, G. Affleck, et al, Adherence with twice-daily dosing of inhaled steroids. Socioeconomic and health-belief differences, *Am. J. Respir. Crit. Care Med.* 157 (1998) 1810–1817.
 - [23] J. Okuno, H. Yanagi, S. Tomura, Is cognitive impairment a risk factor for poor compliance among Japanese elderly in the community?, *Eur J. Clin. Pharmacol.* 57 (2001) 589–594.
 - [24] F.A. Kaona, M. Tuba, S. Siziya, et al, An assessment of factors contributing to treatment adherence and knowledge of TB transmission among patients on TB treatment, *BMC Public Health* 29 (2004) 68.
 - [25] M.R. DiMatteo, Patient adherence to pharmacotherapy: the importance of effective communication, *Formulary* 30 (1995) 596–598.
 - [26] N.M. Clark, J.A. Dodge, Exploring self-efficacy as a predictor of disease management, *Health Educ. Behav.* 26 (1999) 72–89.
 - [27] R.R. Rubin, Adherence to pharmacologic therapy in patients with type 2 diabetes mellitus, *Am. J. Med.* 118 (2005) 27s–34s.
 - [28] C.K. Tebbi, Treatment compliance in childhood and adolescence, *Cancer* 71 (1993) 3441–3449.
 - [29] S.A. Eisen, D.K. Miller, R.S. Woodward, et al, The effect of prescribed daily dose frequency on patient medication compliance, *Arch. Intern. Med.* 150 (1990) 1881–1884.
 - [30] B.G. Bender, S.E. Bender, Patient-identified barriers to asthma treatment adherence: responses to interviews, focus groups, and questionnaires, *Immunol. Allergy Clin. N. Am.* 25 (2005) 107–130.
 - [31] M. Iskudjian, T.R. Einarson, L.D. MacKeigan, et al, Relationship between daily dose frequency and adherence to antihypertensive pharmacotherapy: evidence from a meta-analysis, *Clin. Ther.* 24 (2002) 302–316.